

administering recombinant human relaxin (H2) to a patient wherein the administering is in a sufficient amount and over a sufficient period of time so as to induce VEGF secretion.

31. (Amended) The method of claim 30 wherein the serum concentration of relaxin is maintained for a period of at least 72 hours.

II. REMARKS

Formal Matters

Claims 23-35 are pending after entry of the amendments set forth herein.

Claims 23-35 were examined and were rejected.

Claims 23, 28, and 31 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claim 23, 28, and 31 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 3, lines 23-25; page 4, line 37 to page 5, line 2; page 5, line 37 to page 6, line 8; and page 11, lines 3-6. Accordingly, no new matter is added by these amendments.

Please replace claims 23, 28, and 31 with the clean version provided above.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Claim objections

Claim 28 was objected to because of a typographical error and a missing word. Claim 28 is amended as noted above, thereby adequately addressing the objection to this claim.

Obviousness-type double patenting

Claims 23-27 were rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-5 of U.S. Patent No. 6,211,147.

Applicants enclose herewith a terminal disclaimer, disclaiming patent term beyond the expiration

date of U.S. Patent No. 6,211,147. Thus, this rejection of claims 23-27 may be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claims 23-27, and 31-33 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

Claim 23

The Office Action stated that claim 23 is vague and indefinite because it is not clear what is being treated or what the effect is.

Without conceding as to the correctness of this rejection, claim 23 is amended to recite "treating a condition amenable to treatment by promoting angiogenesis."

Claim 31

The Office Action stated that claim 31 is indefinite because it is not clear what "a period of up to at least 72 hours" means.

Without conceding as to the correctness of this rejection, claim 31 is amended to recite "a period of at least 72 hours."

Applicants submit that the rejection of claims 23-27, and 31-33 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §102(b)

Claims 23, 24, 26, 28-32, and 34 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Cronin et al. (U.S. Patent No. 5,166,191; hereinafter "Cronin").

The Office Action stated that Cronin teaches administering H2 human recombinant relaxin by osmotic pump to rats for at least 72 hours at a dose of 10 ng/min. The Office Action stated that the method of Cronin would inherently induce VEGF secretion. Applicants respectfully traverse the rejection.

The instant claims are directed to a method for treating a disorder amenable to treatment by

promoting angiogenesis, wherein the condition is selected from the group consisting of an infection, and an ischemic wound; and a method for inducing secretion of VEGF. Cronin neither discloses nor suggests the instant methods as claimed.

Cronin discusses use of relaxin to increase cardiac output by increasing the rate and force of atrial muscle contraction. Nowhere in Cronin is there any mention or suggestion that relaxin promotes angiogenesis, or that relaxin induces secretion of VEGF. Without the knowledge provided in the instant specification, those skilled in the art, from reading Cronin, would not have known that relaxin promotes angiogenesis and induces VEGF.

The Office Action stated that the method of Cronin would inherently induce VEGF secretion.

According to the law, a reference may anticipate a claim even if a feature recited in the claim is not specifically disclosed in the reference. However, where the reference is silent as to a specific limitation in the claims, such a gap in the reference must be filled with recourse to extrinsic evidence in order for the reference to serve as an anticipatory reference by inherency. Such evidence must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, *and that it would be so recognized by persons of ordinary skill in the art* at the time the invention was made.¹ The characteristic must flow *undeniably and irrefutably* from the express disclosures of the prior art reference. Mere possibilities or even probabilities are not enough to support a finding of anticipation.²

In relying upon a theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art.³

The Office Action has provided no basis in fact and/or technical reasoning to support a determination that induction of VEGF necessarily flows from the teaching of Cronin. Indeed, until

¹*Continental Can Co. USA, Inc. v. Monsanto Co.*, 20 USPQ2d 1746, 1749-1750 (Fed. Cir. 1991). In this case, a summary judgement of inherency anticipation was deemed improper because of a material fact issue whether a prior art reference's process *necessarily* produced the claimed invention's features.

²*Motorola, Inc. v. Interdigital Technology Corp.*, 43 USPQ2d 1481 (Fed. Cir. 1997)

³*Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inf. 1990)

Applicants made the unexpected observation that relaxin induces VEGF and promotes angiogenesis, those skilled in the art were unaware of this property of relaxin. It does not necessarily flow, from a teaching that relaxin increases the rate and force of atrial contraction, that relaxin induces VEGF secretion and promotes angiogenesis. Accordingly, Cronin cannot anticipate the instant invention as claimed.

Applicants submit that the rejection of claims 23, 24, 26, 28-32, and 34 under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §103

Claims 23-35 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Bigazzi et al. (U.S. Patent No. 5,952,296; hereinafter "Bigazzi") in view of Hudson et al. (U.S. Patent No. 5,023,321; hereinafter "Hudson"), Bryant-Greenwood ((1982) *Endocrin. Rev.* 3:62-90), Wong et al. (U.S. Patent No. 5,023,088; hereinafter "Wong"), and Applicant's admission in the specification in Example 4.

The Office Action stated: (1) Bigazzi teaches administration of relaxin to a human patient in an amount effective for dilation of blood vessels; (2) Bigazzi does not specifically teach maintaining a serum concentration of relaxin of at least 1 ng/nl, use of recombinant H2 relaxin, administration by an osmotic pump, or administration at a progressively diminishing rate; (3) Bigazzi does not teach induction of VEGF; (4) Hudson teaches making human recombinant relaxin H2; (5) Bryant-Greenwood discusses problems associated with purification of natural relaxin; (6) Wong teaches a multi-chamber osmotic pump; and (7) Applicant admits that relaxin in a concentration as low as 1 ng/ml stimulates VEGF. The Office Action concluded that it would have been obvious to administer relaxin by the method of Bigazzi, and to use recombinant relaxin. Applicants respectfully traverse the rejection.

The Office Action has not established a prima facie case of obviousness.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992). Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986). Finally, the prior art reference, or references when combined, must teach or suggest all the claim

limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974). All three criteria must be met. If any one of these criteria is not met, a *prima facie* case of obviousness has not been established.

There is no motivation to combine the reference teachings.

As the Office Action acknowledged, Bigazzi discusses use of relaxin to dilate blood vessels. There is no teaching or suggestion in Bigazzi that relaxin induces secretion of VEGF, or that relaxin promotes angiogenesis. Thus, Bigazzi cannot have provided a motivation to combine the reference teachings.

None of the secondary references make up for the deficiencies of Bigazzi. Hudson merely discusses making recombinant human relaxin. Bryant-Greenwood merely discusses difficulties of using naturally-occurring relaxin. Wong merely teaches use of an osmotic pump. None of the secondary references makes any mention whatsoever of the use of relaxin to induce secretion of VEGF or use of relaxin to treat disorders amenable to treatment by promoting angiogenesis.

There is no reasonable expectation of success.

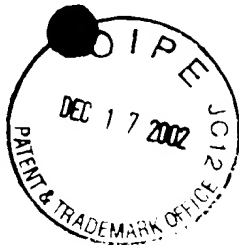
Because neither Bigazzi nor any of the secondary references teaches or suggests use of relaxin to induce secretion of VEGF or use of relaxin to treat disorders amenable to treatment by promoting angiogenesis, there cannot have been a reasonable expectation of success that administering relaxin would induce secretion of VEGF or that administration of relaxin would promote angiogenesis.

The reference teachings do not disclose or suggest all of the claim limitations.

As discussed above, there is no disclosure or suggestion in Bigazzi, nor in any of the secondary references, of a method of inducing secretion of VEGF. As discussed above, there is no disclosure or suggestion in Bigazzi, nor in any of the secondary references, of a method of treating a disorder amenable to treatment by promoting angiogenesis. Accordingly, the cited references do not teach all of the claim limitations.

The Office Action stated that the method of Bigazzi would have necessarily lead to secretion of VEGF by relaxin at the amount administered by Bigazzi. However, the Office Action has provided no basis in fact or technical reasoning for this assertion. Those skilled in the art would not have recognized, from reading Bigazzi, that relaxin necessarily induced secretion of VEGF or that relaxin necessarily

promoted angiogenesis.



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Applicants submit that the rejection of claims 23-35 under 35 U.S.C. §103 has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.


III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CONN003CON.

Respectfully submitted,
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Date: Dec. 12, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the amendments to claims 23, 28, and 31, as shown below.

23. (Amended) A method of [treatment] treating a condition amenable to treatment by promoting angiogenesis, the method comprising:

administering recombinant human relaxin (H2) to a patient at a predetermined rate so as to maintain a serum concentration of at least about 1 ng/ml;

continuing the administration over a period sufficient to [obtain a therapeutic effect on the patient] promote angiogenesis and treat the condition, wherein the condition is selected from the group consisting of an infection, and an ischemic wound.

28. (Amended) A method of inducing secretion of vascular endothelial growth factor (VEGF), comprising the [stpes] steps of:

administering recombinant human relaxin (H2) to a patient wherein the administering is in a sufficient amount and over a sufficient period of time so as to induce VEGF secretion.

31. (Amended) The method of claim 30 wherein the serum concentration of relaxin is maintained for a period of [up to] at least 72 hours.

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